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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 02/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/518,817	BAILEY ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 9-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 9-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response, which included addition of new claims 11-16, cancellation of claim 7 and amendment to claims 1, 2, 6, 9 and 10, filed on 12/1/2005, is made of record. Claims 1-6 and 9-16 are now pending.

In view of applicants' response the following rejection apply.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 10-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Any claim not specifically rejected is rejected as it is dependent o n a rejected claim and shares the same indefiniteness.

1. Recitation of " A method of administering a compound to mammal" in the currently amended claim1, and 10 renders these claims and their dependent claims indefinite, as it is not clear whether what is the method and what for it is administered , whose in need of . As recited , these claims imply , the compound is administered by a method the for a unknown purpose . In addition, claim 1 lacks an therapeutically effective amount.

2. Amendment to claim 2 which now reads A is CH, NH R^2..." renders claim 2 indefinite. Note as elected X is CA and therefore A will be C-CH etc an appropriate correction is needed.

3. Claims11-16 are indefinite as claim 11 lacks an therapeutically effective amount.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 10 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating rheumatoid arthritis, does not reasonably provide enablement for treating any or all disease or disorders mediated by cathepsin S and cysteine protease. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims.

The instant method of use claims 1-6 and 10 are drawn as reach through claims based on the mode of action of instant compounds as cathepsin S and cysteine protease inhibitors. A reach through claim is a claim wherein a mode of action of a genus of compound is disclosed and then based on the mode of action treatment of any or all diseases mediated through the mode of action is claimed. In the instant case, based on the mode of action of instant compounds as cathepsin S and cysteine protease inhibitors treatment of any or all diseases and disorders is embraced in the claim language. The scope of the claims includes as recited any or all diseases including inflammation and immune disorders such as asthma, rheumatoid arthritis, COPD, multiple sclerosis, Crohn's disease, Alzheimers and pain, such as nemopathic pain, which is not adequately enabled solely based on the activity of the compounds provided in the specification. The instant compounds are disclosed to have cathepsin S and cysteine protease inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which applicants provide

no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as cathepsin S and cysteine protease inhibitor that would be useful for all sorts of diseases including inflammation and autoimmune diseases. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as multiple sclerosis, Alzheimer's disease etc,. are very difficult to treat and despite the fact that there are many compounds which act are known to act on "inflammation".

The scope of the claims involves thousands of compounds of claims 1 and 7 as well as the thousand of diseases embraced by the reach through claim language.

In addition, claim 10 is deemed as reach through claim wherein a mode of action is recited first and then all or any diseases that relate to the mode of action is claimed. In the instant case because of the mode of action as cathepsin S and cysteine protease inhibitor, the instant compounds are implied to be useful for treating any or all diseases .

No compound has ever been found to treat diseases of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of modern medicine. Thus, it is beyond the skill of physician today to get an agent to be effective against all diseases generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ

288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Hou et al. Arthritis & Rheumatism, 46(3): 663-674, 2002.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating disorders/diseases that require cathepsin S and cysteine protease inhibitory activity.

2) The state of the prior art: Recent publications expressed that the cathepsin S and cysteine protease inhibition effects are unpredictable and are still exploratory. See Hou et al., cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical

use for r treating any or all cancers or abnormal cell growth of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all cancers or abnormal cell growth and the state of the art is that the effects of cathepsin S and cysteine protease inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all diseases including those yet to be related to cathepsin S and cysteine protease .

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

This rejection is same as made in the previous office action . It is maintained as amendment claims 1-6 and 10 appear treat something by administering the compound of formula I to mammal .

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 and 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altman et al. WO 03/020278.

Altman et al. teaches several variously substituted 2-cyano-pyrimidine compounds for treating rheumatoid arthritis, which include compounds, and the method of use of claimed in the instant claims. See page 1, formula I and note when R choice is OR4 or NR3R4 and R1 is CH_2NR5R6, compounds taught by Altman et al., includes instant compounds. See pages 1-16 for details of the invention and pages 17-52 for examples of various compounds made.

Although Altman et al., exemplifies large number of 2-cyanopyrimidine compounds, all of them are limited to R =H, not OR4 or NR3R4. However, Altman et al. teaches the equivalency of those compounds exemplified with specific substituents with that generically recited for compound of Formula I in page 1.

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make 2-cyanopyrimidine compounds variously

substituted with R, R1 and R2 including R = OR4 or NR3R4 as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

This rejection is same as made in the previous office action but now includes newly added claims 11-16.

Applicants' argument to overcome this rejection is not persuasive.

First of all claim 9 is a pharmaceutical composition claim. A pharmaceutical composition is a pharmaceutical composition irrespective of its intended use as they rely on the same active ingredient. Note there is no material difference between these claims as they rely on the same scope of active ingredient. Different intended use in such claims are given no material weight. Note In re Tuominen 213 USPQ 89.

Secondly, contrary to applicants urging that that Altman is limited to the compounds he had exemplified , Altman et al., is entitled to the broader scope of compound of formula I as much as applicants are entitled to scope embraced for compound of formula I and not limited by the limited species made.

Thirdly, Altman et al. clearly teaches equivalency of exemplified compounds with those generically claimed. The fact that Altman teaches mostly R=H by no means would deter the scope generically embraced. Since Altman et al., permits R = H, R4, OR4, NR3R4, one trained in the art would know that these groups are equivalent as for as the desired activity is concerned and would be motivated make the entire series as he would expect that the compounds of these series will have the same utility taught by the reference. The same applies to instant claims wherein R, X and R^1 have different

choices but not all are exemplified. Hence, the case law cited by the applicants- In re Piasecki, 223 U.S.P.Q. 785, 788 (Fed. Cir. 19M), Karsten Mfg. Corp. v. Cleveland Gulf Co., 242 F.3d 1376. 1385, 58 U.S.P.Q.2d 1286, 1293 (Fed. Cir. 2001), Amgen, Inc. v. Chugai Pharm. C0.. 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).and In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970) are not to the point. There is an equivalency teaching and hence a expectation of success. There is no hind sight analysis as Altman et al., teaches suitable R choices and all the limitations are clearly embraced in these definitions.

Fourthly, there is no reason to believe that the preferred embodiments are the only compounds one should consider for prior art purposes. The fact that Altman et al. claims a preferred embodiment does make the teaching of the genus immaterial. Again if such is the case applicants invention should also be limited to species made not the genus. In this regard applicants' attention is drawn to In re Bruckel which states " References must be considered under 35 U.S.C 103, not only for what it expressly teaches but also for what it fairly suggests; all disclosures of prior art, including unpreferred embodiments must be considered in determining obviousness". In re Bruckel, 201 USPQ 67.

As for the applicants' assertion that instant invention is limited to Cathespsin S while Altman et al., teaches Cathepsin K, as noted in the instant specification Cathepsin S belongs to same family of cysteine proteases as Cathepsin K. See page 1, lines 10-11. In addition, instant specification also recites the intended use of the instant compounds is for inhibition of cysteine protease. See page 7, lines 9-10 and 20-21.

Thus, applicants' assertion that instant invention is limited to Cathepsin S only lack factual support in the specification. In addition, there is no showing that instant compound only inhibits Cathepsin S only not any other member of the cysteine proteases including Cathepsin K. Furthermore irrespective of the mode of action, both prior art compounds and instant compounds are useful for treating rheumatoid arthritis. Thus the method of use is same.

Finally, one trained in the art would make the compounds of Altman et al., for inhibiting Cathepsin K and therefore for treating rheumatoid arthritis.

Hence, this rejection is proper and is maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Acting Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson whose telephone number is (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

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2/16/2006